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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,073	11/14/2001	David Botstein	P2730P1C15	4049

35489 7590 10/05/2006

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,073	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *122-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *122-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/5/2006 has been entered.

Claims 122-126 and 129-131 are pending and under consideration. No claim has been amended.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-126 and 129-131 are rejected under §35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

This rejection is maintained for reasons of record at pages 3-5 of the Examiner's Answer mailed 4/10/2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 122-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

This rejection is maintained for reasons of record at pages 6-8 of the Examiner's Answer mailed 4/10/2006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 122-126 and 129-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over clone H74302, isolated by L. Hillier et al., WashUMerck EST Project 1995 in view of Sibson et al., WO94/01548.

This rejection is maintained for reasons of record at pages 8-9 of the Examiner's Answer mailed 4/10/2006.

Response to Arguments

Applicants arguments filed 7/5/2006 are largely cumulative and duplicative of the arguments made in the Appeal Brief, and were fully responded to in the Examiner's answer, mailed 4/10/2006. The most notable addition is the second Polakis declaration, filed 7/5/2006, signed 3/29/2006.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

The Polakis II declaration has been fully considered to the following effect:

In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. (1) Dr. Polakis declares that 28 of 31genes identified as being detectably over expressed at the mRNA level were found also to have increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO809 (i.e., data regarding amplification of PRO809 genomic DNA), and does not disclose any information regarding PRO809 mRNA levels. This was the main issue with the first Polakis declaration, and remains pertinent; there is no demonstration of *any* mRNA level for PRO809, hence the theoretical correlation of mRNA with protein is not probative. The fact that needs to be established here is that a ΔCt value of at least 1.0 would be predictive of increased protein expression. Applicants have never addressed this point directly. Furthermore, there is strong opposing evidence showing that *gene amplification is not predictive of increased mRNA levels* in normal and cancerous tissues See, e.g., Pennica et al., discussed in the Examiner's Answer. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by

the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data refer to the mRNA's in question only by UNQ numbers; UNQ464, which is PRO809, is not represented, and declarant provides no information about the sequences that *are* represented; the assertion in the specification is that PRO809 was found to be amplified approximately two fold in 3 of 10 human lung tumor squamous cell carcinoma cell lines, 2 of 9 human lung tumor adenocarcinoma cell lines, and the sole human lung tumor large cell carcinoma cell line. It is not clear whether any or all of these tissues were represented in the data. There is no indication of *how much* the mRNA and protein were overexpressed, as there is no actual description of the experiment that was done, but rather a conclusory statement as to what was measured, and what it means.

For the reasons above, the Polakis II declaration is not sufficient to overcome the rejection of claims 122-126 and 129-131 under 35 U.S.C. §101 and §112, second paragraph.

The Examiner notes that the two Polakis declarations are not consistent:

In the first declaration, Dr. Polakis declares that "we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells". In the second, he states that "we have identified approximately 200 gene transcripts that are present in human tumor ***tissue*** at significantly higher levels than in corresponding normal human ***tissue***."

In the first declaration, Dr. Polakis declares that "In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells." In the second, he states that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue <u>at the mRNA level,</u> 28 of them (i.e. greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue <u>at the protein level.</u>"

It cannot be determined whether the two declarations are referring to the same data set, or different data sets. Further, there has been no explanation of why the Declarant now refers to tumor *tissue* rather than tumor *cells,* nor what the perceived significance of this change is.

Addressing the remainder of applicants arguments:

A number of applicants arguments continue to be directed at the predictability of protein levels when *mRNA* levels are amplified. The Examiner maintains that the most significant issue in this case is that the data are drawn to *genomic* data, and *not* mRNA data. While the Examiner concedes that if *mRNA* levels were shown to be significantly higher in a significant proportion of a given tumor type that such would be indicative of utility for the claimed antibodies, she maintains that such is not predictable based upon the data in the specification, which are specifically drawn to amplification of *genomic* DNA.

At pages 5-7 of the response, Applicant discusses newly submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration; (point (ii) below). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. First and foremost, the Examiner reiterates that the issue here is not predictability of protein based upon amplified mRNA, but rather that the specification does not measure mRNA, but rather genomic DNA, and that the levels of genomic DNA amplification are completely consistent with the expected aneuploidy associated with cancer, and that it is not predictable, and is in fact unlikely that such levels of genomic amplification would be associated with a measurable increase in protein levels. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including

translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

"The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

With the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Hu (2286 genes) (cited previously by Examiner).

In response to applicants discussion of the Orntoft reference, the Examiner reiterates what was stated in the Examiner's Answer: "Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein."

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification (and for reasons cited above do not merit further discussion), a single reference, that by Godbout, is pertinent to the issue at hand. However, the Examiner finds applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO809 on the basis of a minor genomic amplification, Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. That result was (apparently, applicants only having submitted the abstract) confirmed. On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO809 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO809 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO809.

In summary, of applicants 148 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO809 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

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studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. That result was (apparently, applicants only having submitted the abstract) confirmed. On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO809 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO809 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO809.

In summary, of applicants 148 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO809 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

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In summary, of applicants 148 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO809 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

The remainder of applicants arguments have been fully addressed of record.

In closing, the Examiner notes that submission of *data* showing PRO809 protein or mRNA to be significantly overexpressed in a significant proportion of samples of any of the tested tumor types would be convincing evidence of utility. However, it remains that aneuploidy is one of the hallmarks of tumor formation, and that the specification as filed shows only levels of genomic amplification consistent with such, and that on the basis of such it is *not* predictable that the PRO809 protein would be overexpressed in the tested cells.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

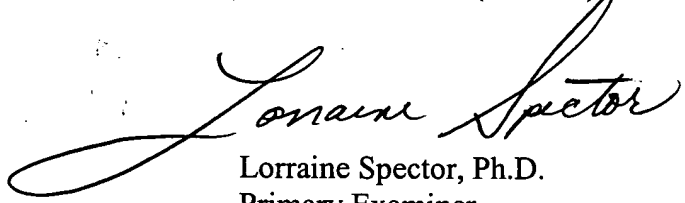
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner